Remarks

Claims 1, 6-10, 12-14, 29, 34-39, 44-49, and 59-68 are pending in the present application. Claims 2-5, 11, 15-28, 30-33, 40-43, and 50-58 were previously canceled in the response dated October 13, 2003. Applicants have hereinabove amended claim 1, 13 and 14. This Amendment adds no new matter to the application. Applicants respectfully request entry of this Amendment and reconsideration of the application as amended.

I. Enablement Rejection Under 35 U.S.C. §112, first paragraph for Claims 1, 6-10, 12-14, 29, 34-39, 44-49, and 59-68

On pages 2-5 of the January, 2004 Action the Examiner has rejected claims 1, 6-10, 12-14, 29, 34-39, 44-49, and 59-68 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is mostly nearly connected, to make and/or use the invention.

Claims 59-68

With regard to claims 59-68, Applicants traverse this rejection. These claims are drawn to a method of treating a hyperproliferative disorder, including cancer.

The Examiner asserts that the claims are interpreted to include any and all disorders associated with angiogenesis, that the specification reads on any and all disorders of cancer or angiogenesis in which cells receive pro-inflammatory signals through vascular endothelial growth factor receptor tyrosine kinase. Citing a publication (Nature, 2000, page 255), the Examiner also asserts that at least as of 2000, much more than routine experimentation would be required to find a compound that will be really effective in treating cancer associated with angiogenesis. The Examiner asserts that as of 2000, there was only the potential, and that success would require future development, i.e., more than routine experimentation. The Examiner also asserts that no evidence of in vitro/in vivo effectiveness is seen in the specification for one, let alone all, of the instant compounds for the uses claimed herein (citing *In re Surrey*, 252 USPQ 724, regarding sufficiency of disclosure). The Examiner asserts that that competent evidence of art-recognized efficiency for intended uses needs to be provided, and that any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the likelihood of *in vivo* use for all uses being claimed (citing Ex parte Powers, 220 USPQ 925).

The Examiner also asserts that the claims embrace the treatment of cancer generally, and that there never has been a compound capable of treating cancer generally. The Examiner asserts that there are compounds that treat some range of cancers, but no one had ever been able to figure out how to get a

compound to be effective against cancer generally, or even a majority of cancers. The Examiner concludes that it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

The Examiner also asserts that the claims covers not only all cancers but also cover any disorders arising from abnormally high rates of proliferation, including precancerous conditions such as different types of abnormal angiogenesis. The Examiner asserts that no agent with anything remotely close to such a scope had ever existed in medicine. He asserts that when the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, and cites *In re Ferens,* 163 USPQ 609. The Examiner also asserts that the failure of a skilled scientist to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioner in that art, citing *Genentech vs. Novo Nordisk,* 42 USPQ2nd 1001, 1006.

For the reasons that follow, applicants respectfully traverse this rejection of claims 59-68, and request that it be withdrawn.

Applicants respectfully submit that the Examiner has failed to make a *prima facie* case of non-enablement for claims 59-68 of the subject application under 35 U.S.C. §112, first paragraph that is well-grounded in scientific reasoning or evidence. The Examiner has failed to set forth a reasonable explanation as to why he believes that the scope of protection is not adequately enabled by the description of the invention provided in the specification. In order to make a §112, first paragraph rejection the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

The CCPA has stated that "it is incumbent upon the Patent Office, whenever a rejection on this basis [35 U.S.C. 112, first paragraph] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 169 USPQ 368, 370 (CCPA 1971). Applicants respectfully submit that the Examiner has failed to meet his burden and has neither provided evidence or reasoning, which would support his assertion that the claims of the subject application are not enabled.

The specification sets forth in detail, on pages 1-2, and 25-26 that the compounds of the present application inhibit the receptor tyrosine kinase and that such activity has been correlated with the

treatment of the various disorders recited in the claims. Applicants state on page 25, line 36 – page 26, line 12 of the present application:

> The compounds of the present invention are inhibitors of the vascular endothelial growth factor receptor ("VEGFR"), erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), *erbB2, HER3,* or *HER4* and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly in humans. The compounds of the present invention are also inhibitors of angiogenesis and/or vasculogenesis. In particular, the compounds of the present invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders such as malignant and benign tumors of the liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, head and neck, and other hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH). It is, in addition, expected that a compound of the present invention may possess activity against a range of leukemias and lymphoid malignancies.

It is well known that inhibition of receptor tyrosine kinases will be useful in the treatment of abnormal cell growth and in particular cancer, as set forth in the above paragraph. Applicants respectfully submit that a large number of compounds having tyrosine kinase inhibitory properties have been identified in the art. In this regard, applicants direct the Examiner's attention to col. 1, lines 20-37 of U.S. Patent 6,492,383 B1 ("'383 patent"), for a list of patent applications disclosing receptor tyrosine kinase inhibitors. More particularly, applicants direct the Examiner's attention to col. 2, line 47- col. 2, line 3 of the '383 patent which has been reproduced below for the Examiner's convenience:

> Receptor tyrosine kinases are large enzymes that span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor, a transmembrane domain, and an intracellular portion that functions as a kinase to phosphorylate specific tyrosine residue in proteins and hence to influence cell proliferation. The foregoing tyrosine kinases may be classified as growth factor receptor (e.g. EGFR, PDGFR, FGFR and erbB2) or non-receptor (e.g. c-src and bcr-abl) kinases. It is

> known that such kinases are often aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial or pancreatic cancer. Aberrant erbB2 activity has been implicated in breast, ovarian, non-small cell lung, pancreatic, gastric and colon cancers. It has also been shown that epidermal growth factor receptor (EGFR) is mutated or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid cancers. Thus, it is believed that inhibitors of receptor tyrosine kinases, such as the compounds of the present invention, are useful as selective inhibitors of the growth of mammalian cancer cells.

Contrary to the Examiner's contention, Applicants respectfully submit that there is a high level of expertise in the field of the present invention. Applicants respectfully submit that the specification of the claimed invention coupled with the high degree of expertise in the field of tyrosine kinase inhibitors enables one of ordinary skill in the art to practice the claimed invention.

The Examiner has offered no objective evidence for his position that the claimed invention is not enabled. The Examiner has merely offered his opinion without any documented support for such a position. The Examiner's position is contrary to the understanding of those of ordinary skill in art as indicated and shown by the multitude of patent applications direct to compound useful in the treatment of hyperproliferative disorders. The specification teaches that all the compounds employed in the pharmaceutical compositions and methods of these claims are inhibitors of the receptor tyrosine kinase and that they are useful in treating the various named disorders and conditions. The Examiner has not proffered any evidence to show that those skilled in the art would doubt the objective truth of these statements. Therefore, such statements must, as indicated above, be accepted as true.

On pages 26-29 of the specification, Applicants provide further guidance for those skilled in the art to assess the activity of the compounds falling within the scope of the present invention using the recited *in vitro* and *in vivo* tests. Moreover, pages 29-31 of the specification describe how the methods of claimed invention can be carried out by those skilled in the art. It specifies, on these pages, appropriate dosages and methods of administration. This description includes the various modes by which the compounds employed in the claimed methods can be administered to mammals, the pharmaceutically acceptable forms in which they can be administered, and appropriate dosages for their administration. The foregoing information is sufficient to enable one skilled in the art to practice the

inventions of each of claims 59-68 and thus complies with the requirements of 35 U.S.C. §112, first paragraph.

A specification disclosure that contains a teaching of the manner and process of making and using the invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Further, the burden is on the Examiner to come forth with evidence to establish a *prima facie* case of non-enablement. *In Re Armbruster*, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975); *In re Marzocchi*, 169 U.S.P.Q. at 370. The Examiner has not proffered any evidence, merely opinion argument for the lack of enablement of the claimed invention.

As discussed above, tyrosine kinase receptors have been studied extensively and their relationship to the onset of cancers has been cataloged and detailed in numerous publications *prior* to applicants' effective filing date of June 6, 2000. Applicants herewith provide a representative sample of the publications linking receptor tyrosine kinase, such as EGFR, erbB2 and VEGF, to a wide variety of diseases, including human cancers. The literature prior to applicants' patent application is replete with evidence of the overexpression of tyrosine kinases in human diseases and of efforts to prevent and treat the diseases using inhibitors of the aberrant tryosine kinase.

It was reported by Kelloff et al., Cancer Epidemiol Biomarkers Prevention, Vol. 5, Issue 8, pages 657-666, in 1996 that epidermal growth factor receptor (EGFR) was selected as a target for drug development for cancer prevention. Kelloff stated that loss of tyrosine kinase regulatory mechanism has been implicated in neoplastic growth and mention in particular the following cancers: (i) bladder, (ii) breast, (iii) cervix, (iv) colon, (v) esophagus, (vi) head, (vii) neck, (viii) lung and (ix) prostate.

Kelloff also stated that several EGFR inhibitors had been synthesized to block the EGFR expression thus functioning as cancer inhibiting agents. Applicants also note that the molecular underpinnings of cancer have evolved significantly in the last 10 years. This evolution has resulted in a much clear understanding of the molecular triggers that result in hyperproliferation of cells, such as the overexpression of the EGFR. This understanding of the molecular basis of cancer has led to a research effort as noted by Kelloff to develop "targeted" therapies to disrupt the signal pathways that result in neoplastic growth. Accordingly, it is reasonable and accepted by those in the art at the time of filing of the subject application that interruption of the overexpression of tyrosine kinase expression such as EGFR and VEGFR, will prevent the growth of cancerous cells. Many different cancers shared a similar molecular basis such as the overexpression of particular receptors such as EGFR.

Prior to applicants' filing of the subject application it was known in and accepted in the art that overexpression of EGFR was not restricted to neoplasms. Expression of the EGFR was reported to involved in benign inflammatory diseases such as chronic pancreatitis (Lemoine et al., J. Pathol., 166, 7-12, **1992**). It has also been reported that abnormal angiogenesis not only plays a major rule in pathogenesis of tumor growth but is also involved in rheumatoid arthritis, atherosclerosis and various retinopathies (Stephan et al., Puerto Rico Health Sciences Journal, Vol. 15, Issue 3, pages 169-178, **1996**). It is stated in col. 2, lines 11-25 of the '383 patent:

> It is known that polypeptide growth factors such as vascular endothelial growth factor (VEGF) having a high affinity to the human kinase insert-domain-containing receptor (KDR) or the murine fetal liver kinase 1 (FLK-1) receptor have been associated with the proliferation of endothelial cells and more particularly vasculogenesis and angiogenesis. See PCT international application publication number WO 95/21613 (published August 17, 1995).

Applicants attach for the convenience of the Examiner a copy of WO 95/21613 referred to in the preceding paragraph. Applicants respectfully submit that the claimed invention is enabled as of its filing date and the Examiner's assertion under 112, first paragraph are unsupported. Furthermore, in view of the art at the time of the filing of the subject application it was accepted by those of ordinary skill in the art that inhibition of receptor tyrosine kinases, such as EGFR, erbB2, and VEGFR would be useful in treatment and prevention of a wide variety of diseases. Applicants have provided the Examiner with a small number of publications prior to the filing date of the subject application showing the state of the art at the time (Appendix A). Applicants believe it is incontrovertible that those of ordinary skill in the art accepted that development of inhibitors of receptor tyrosine kinases would be useful in the treatment of the diseases recited in the claims of the subject application. The Examiner has offered no objective evidence, which would contradict or question this understanding in the art at the time the filing of the subject application. Applicants respectfully request that the Examiner reconsider and withdraw his rejection of claims 59-68 under 35 U.S.C. §112, first paragraph for the reasons set forth above.

Claims 1, 6-10, 12-14, 29-34 and 44-49

On pages 4-5 of the Action the Examiner maintained his rejection of the use of the term "prodrug" in claims 1, 6-10, 12-14, 29, 34-39, and 44-49 under §112, first paragraph for the reasons of record. The Examiner has considered Applicants' arguments that the specification provides a definition

for the term "prodrug" on pages 17 and 18, including Applicants excerption of this section of the specification in their arguments. However, the Examiner has maintained that the definition still could not be found on these pages. Applicants continue to assert that a definition has indeed been provided on pages 17 and 18 as excerpted in Applicants' remarks in the Amendment filed on October 13, 2003. The Examiner continues to assert that the term is still too broad to enable one skilled in the art to determine how the prodrug is converted to active compounds, by what mechanisms and what site the prodrug will be active, what in vivo enzymes are likely to be involved in cleaving the protected group. The Examiner concludes that all these factors are uncertain and require one skilled in the art to spend undue amount of time to practice the invention.

Applicants respectfully continue to disagree with the Examiner's position in rendering a §112, first paragraph enablement rejection for the reasons of record, and incorporate by reference their detailed remarks from the Amendment filed October 13, 2003. Nevertheless, to advance prosecution, Applicants have amended claims 1, 13 and 14 to delete the term "prodrug" or "prodrugs". Applicants respectfully submit that this amendment overcomes the present rejection.

II. <u>Rejections under 35 U.S.C. §112, Second Paragraph</u>

On pages 5-6 of the Action the Examiner states that maintains his rejection of 1-4, 15-18, 30-32 and 40-42 under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. However, Applicants respectfully direct the Examiner's attention to the fact that of these claims, only claim 1 is currently pending. Claims 6-10, 12-14, 29, 34-39, and 44-49 ultimately depend from claim 1. Applicants respectfully request the Examiner to clarify which claims he is actually rejecting under 35 U.S.C. §112, Second Paragraph. Is the Examiner only rejecting claim 1 and objecting to the other claims as being dependent upon a rejected base claim (claim 1)? The Examiner is respectfully requested to clarify this issue.

The Examiner states that for the word "heterocyclic," the Applicants argue that these terms are defined in the specification and thus definite in light of the specification. However, the Examiner asserts that reading a claim in light of the specification is quite different from reading the limitations of the specification into the claim, and cites *In re Prater,* 415 F.2nd 1393, 162 USPQ 541. The Examiner asserts that the claims themselves do not carry the limitation as specified in the specification. The Examiner further asserts that when the claims having these phrases are given the broadest interpretation, they are still open-ended in terms of the array of heteroatoms, size of the rings, as well as nature of atoms as ring members.

Applicants respectfully continue to traverse the Examiner's rejection of claim 1 under 35 U.S.C. §112, second paragraph for reasons of record, and incorporate by reference their detailed remarks from the Amendment filed on October 13, 2003.

Applicants reiterate that the legal standard for determining whether particular claim language is sufficiently "definite" depends on whether one skilled in would understand the scope of that claim language when read in light of the patent specification. See, *Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 USPQ2d 1081 (Fed. Cir. 1986); Seattle Box Co. v. Industrial Crating & Packing Inc., 221 USPQ 568, 574 (Fed. Cir. 1984); In re Morasi, 218 USPQ 289, 292 (Fed. Cir. 1983).* Furthermore, as pointed out by the Applicants in their excerpt from the Federal Circuits decision on Shatterproof Glass "if the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." It is respectfully submitted that present claim 1, when read in the light of the specification reasonably apprise those of ordinary skill in the art both the utilization and the scope of the invention.

Applicants respectfully point out that the term used in the claims which the Examiner should be focusing on is not only the term "heterocyclic", but rather the term "heterocyclic"u modified as a "5 to 10 membered heterocyclic". Furthermore the phrase "5 to 13 membered heterocyclic" has been deleted in amended claim 1. The specification clearly sets forth on page 16, lines 21-26 the meaning of "5 to 10 membered heterocyclic":

> The term "5 to 10 membered heterocyclic" or "5 to 13 membered heterocyclic", as used herein, unless otherwise indicated, means aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 5 to 10 or 5 to 13 atoms in its ring system.

Applicants respectfully submit that the definition of the term "5 to 10 membered heterocyclic" is patently clear to one of ordinary skill in the art based upon the above disclosure, the high level of skill in the art, the well known use of the term "heterocyclic". Applicants further assert that the term "5 to 10 membered heterocyclic" in the claim when read in light of the disclosure in the specification is **not** open-ended in terms of the array of heteroatoms, size of the rings, as well as nature of atoms as ring members. Nothing further is required. Applicants are not required to provide a blueprint. Well known terms of art do not require further definition than what has already provided by the Applicants. Applicants therefore respectfully request the Examiner to withdraw the present rejection.

Conclusion

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for rejection set forth in the January 22, 2004 Office Action and earnestly solicit allowance of the claims pending in the subject application.

Respectfully submitted,

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Appendix A

(List of technical references cited in this response; copies of nonpatent references provided)

1. U.S. Patent 6,492,383 B1.
2. Cancer Epidemiol Biomarkers Prevention, Vol. 5, Issue 8, pages 657-666.
3. Lemoine et al., J. Pathol., 166, 7-12, 1992.
4. Stephan et al., Puerto Rico Health Sciences Journal, Vol. 15, Issue 3, pages 169-178, 1996.
5. WO 95/21613.